

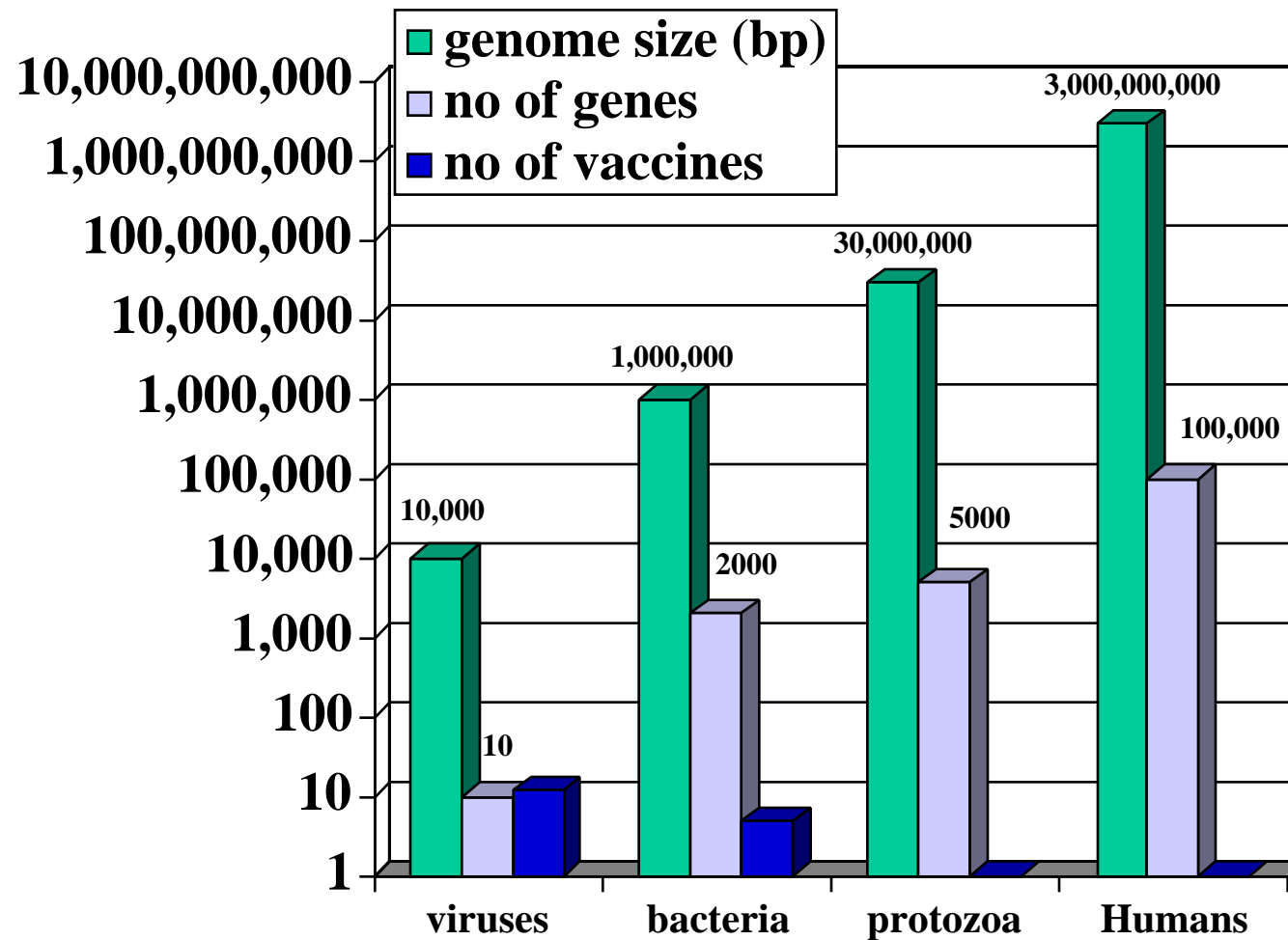
21th Century BioMedicine: Genomes to Vaccines and Drugs

CDR Daniel J. Carucci, MD, PhD

Malaria Program

Naval Medical Research Center

Complex organisms require complex solutions



Vision:

thinking into 21st century

- Completing the genomes of *Plasmodia* will provide the foundation for all future malaria research.
- We have an obligation to conduct functional genomics research to exploit these sequence data for vaccine and drug development.
- The enormous quantity of data that are generated from these studies require the implementation of powerful, scalable bioinformatics capabilities.
- Will provide foundation for future infectious disease and bio-defense research.

Malaria Genome Project: Objectives

- Complete and annotate the genomic sequence of *P. falciparum*
- Produce substantial amounts of genomic sequence data from *P. vivax*
- Make genome sequence data readily available via Internet
- Develop methods for exploiting genomic sequence data for vaccine and drug development

Funding and Timeline

- FY97: \$1 million start up funds (NIAID) to TIGR/NMRC
- 1997: TARA recommends funding Malaria Genome Project
- Initiated by DDR&E, creation of new STEP (Malaria Genome Sequencing)
- DoD (USAMRMC) funding about \$1.4 million/year (6.1)
 - TIGR sequencing contract
- Leveraged funds from major funding agencies (\$24M)
 - Burroughs Wellcome Fund, NIH and the Wellcome Trust (UK)
- 1998: Publication of first-ever complete chromosome sequence from malaria in *Science*
- 1999: Functional genomic studies well underway



Chromosome 2 Sequence of the Human Malaria Parasite *Plasmodium falciparum*

Malcolm J. Gardner, Hervé Tettelin, Daniel J. Carucci,
Leda M. Cummings, L. Aravind, Eugene V. Koonin,
Shamira Shallom, Tanya Mason, Kelly Yu, Claire Fujii,
James Pederson, Kun Shen, Junping Jing, Christopher Aston,
Zhongwu Lai, David C. Schwartz, Mihaela Pertea,
Steven Salzberg, Lixin Zhou,* Granger G. Sutton,†
Rebecca Clayton, Owen White, Hamilton O. Smith,†
Claire M. Fraser, Mark D. Adams,† J. Craig Venter,†
Stephen L. Hoffman‡

Chromosome 2 of *Plasmodium falciparum* was sequenced; this sequence contains 947,103 base pairs and encodes 210 predicted genes. In comparison with the *Saccharomyces cerevisiae* genome, chromosome 2 has a lower gene density, introns are more frequent, and proteins are markedly enriched in nonglobular domains. A family of surface proteins, rifins, that may play a role in antigenic variation was identified. The complete sequencing of chromosome 2 has shown that sequencing of the A+T-rich *P. falciparum* genome is technically feasible.

Impact of these early results

- Malaria genome sequence data has already greatly accelerated malaria research
- Two major publications (PNAS, Science) on discovery of novel biochemical pathways for drug development
- Fed research pathways for both malaria vaccine and drug development within DoD and outside.
- Provided infrastructure for development of entirely new approaches to malaria research.

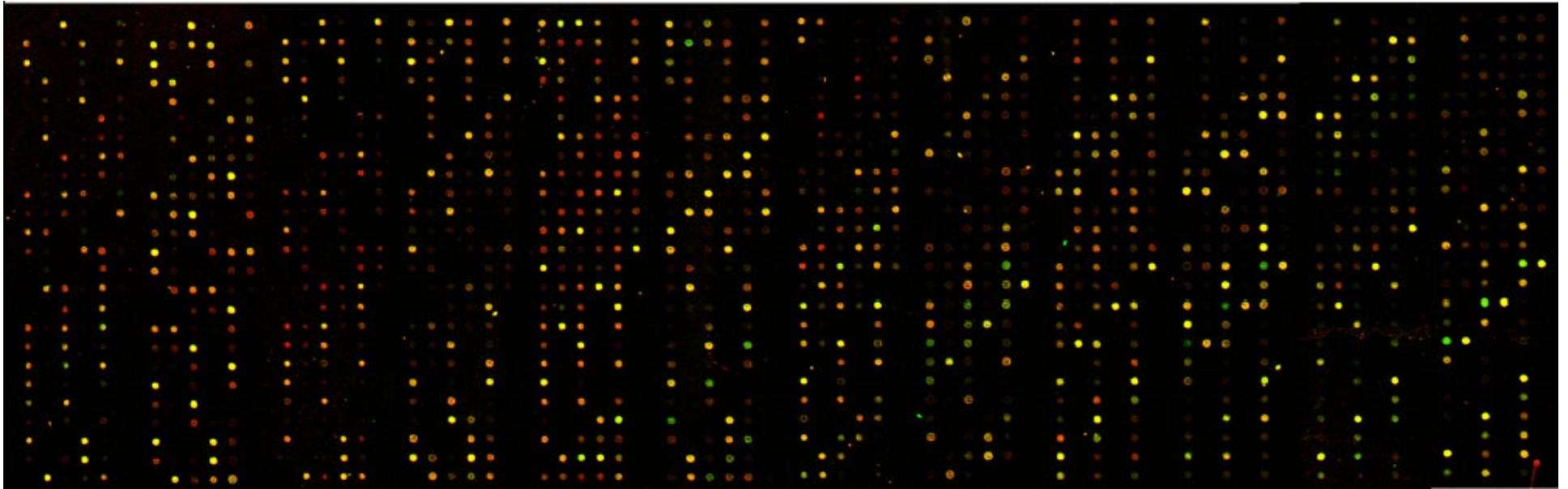
DoD is at the cutting edge of technologies for turning genomes into new vaccines and drugs

- DNA microarrays
- High throughput proteomics
- Powerful scalable relational databases

DNA microarrays

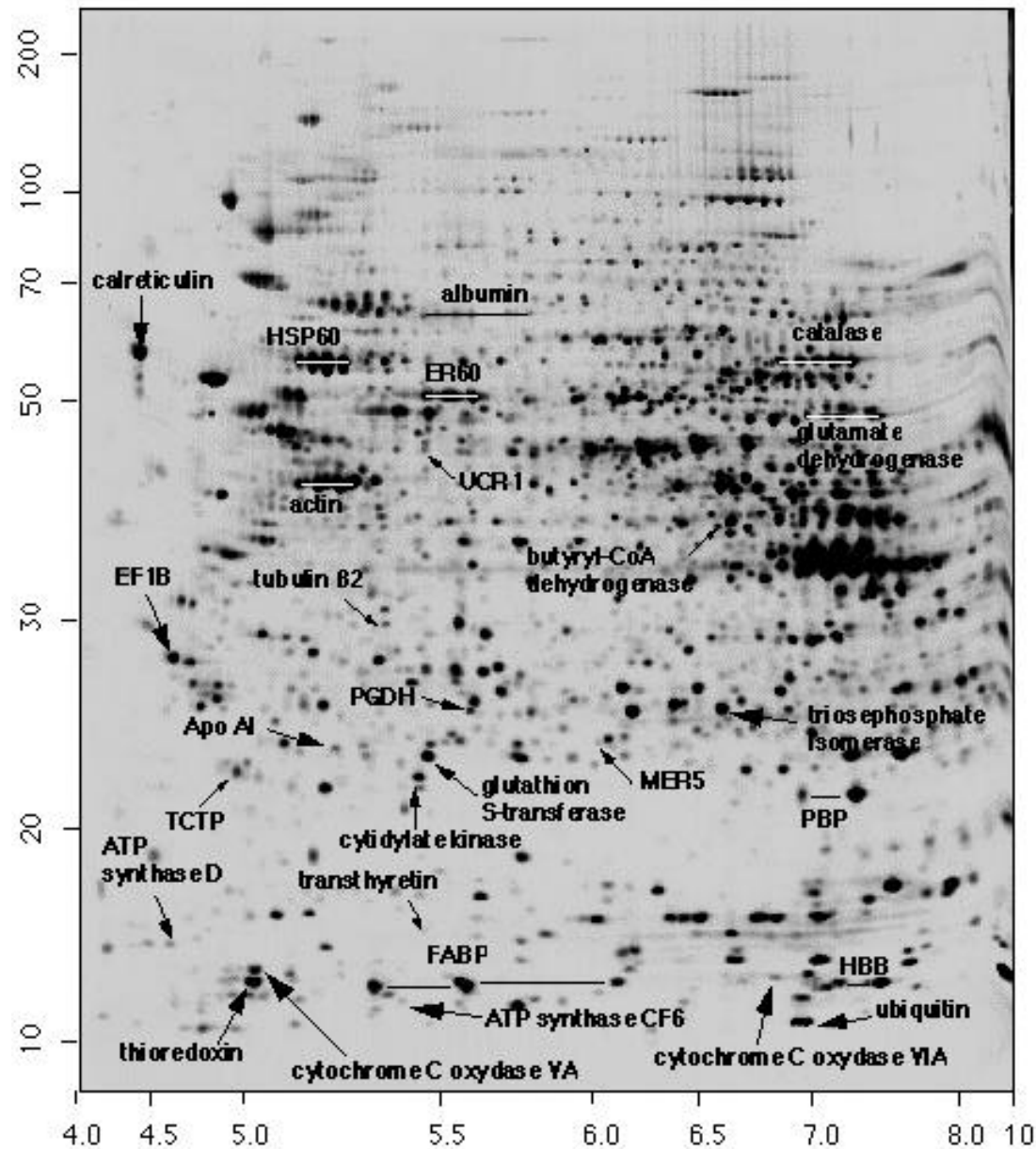
- 10,000 genes on single glass slide
- Measure gene expression of entire genomes overnight
- Generates hundreds of thousands of data points per experiment
- Simple and easy to deploy

First-ever *P. falciparum* chromosome microarray



Malaria Program
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"Traditional Proteomics"



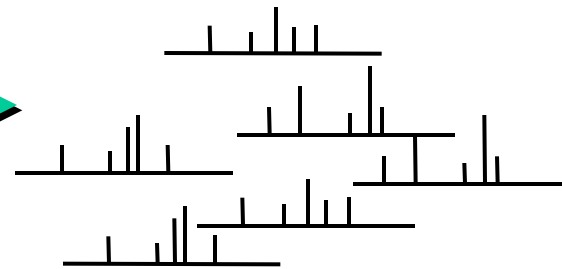
P. falciparum sporozoites,
liver stage schizonts, blood
stage schizonts

High throughput mass spectrometry

Combined liquid chromatography/
mass spectrometer



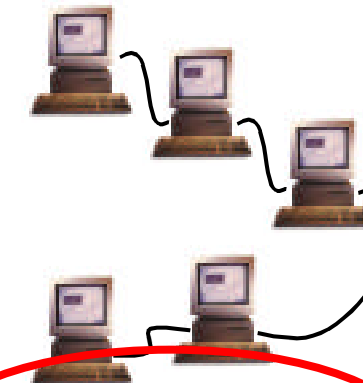
Mass spectra



locus	peptide
MP01002	DDSATGFAGDLNDDCKNAHIFKAFREDVWTCGKVC
MP01002	EFLGLLNNETTCTKKLND
MP01002	AMVCALTYEECTSSASGGEKNTTITQDDGLKGALIK
MP01110	KGNSKSNFIFPRD
MP01110	KNISKVCQNKSTINVPKV
MP01110	ESGAIINNNDNQHNNV
MP01118	KQYEQIRQNEKI
MP03005	KEAADVAEEAARE
MP03006	SICSQSVEPQVVSQSQDKM
MP03030	LMEYQKIISDKITSGISNNMKDI
MP03030	KNTKRYRKS
MP03030	KQVCVFCKKT
.	-
.	-
MP03064	DSISSINNINNINNINNINNINNI
MP03077	FQFINYNIVKEK
MP03083	QTKETNITITCILIKLISNVL
MP03099	YKNGDIYNMEIINNVDNIH
MP03100	RRKLCCLGERGDYKQ
MP03105	NYYYNNLCDGDNNKNEVN
MP03118	KVEKMSAEQQRKYEKK
MP03121	DNEWNTLKHDFISQYLQSEQPN
MP03121	CVNICGVDVCGLKKGDNNGELDDKQIILVRALIK
MP03129	NDNITLCVNNSNELYLYN

"Summary" and
"Autoquest"
software

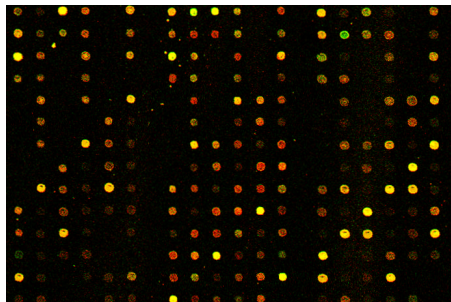
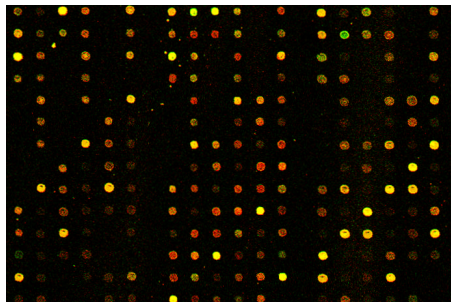
Sequest®
software



Genomic database

Results of High throughput mass spectrometry (HTMS)

- Previously only five sporozoite vaccine antigens discovered in 15 years of research.
- In only 2 months, have identified over 100 new potential antigens with HTMS and genome sequence data.
- Potential to provide foundation for all vaccine candidate discovery.



A diagram illustrating a peer-to-peer network topology. Four identical desktop computers are arranged in a vertical column. Each computer consists of a monitor, a system unit, and a keyboard. The monitors display a grid-like interface. On the left side, three black arrows point towards the computers: one towards the top computer, one towards the middle computer, and one towards the bottom computer. On the right side, a single black arrow points away from the group of computers. A series of curved grey lines connect the computers in a mesh-like fashion, representing a decentralized network structure where each node can communicate with multiple other nodes.

Image color correction application

Spot Information

Color name: 1. cyan color correction
 Name: CMYK 100

	Channel 1	Channel 2	Channel 3
Method 1	CMYK 100	CMYK 100	CMYK 100
Method 2	CMYK 100	CMYK 100	CMYK 100
Method 3	CMYK 100	CMYK 100	CMYK 100

Close (F5) button

CMYK 100 CMYK 100 CMYK 100

Close Print Full screen Exit

Summary (in 3 years)

- Genomic sequencing
 - Established feasibility, set the standard for others
 - Genome will be completed within ~18 months
 - Publications in Science, Nature, etc
 - Two provisional patent applications
- DNA microarrays
 - Constructed first-ever chromosome-specific microarrays, ready for scale up
- High-throughput mass spectrometry
 - Identification of over 100 new potential sporozoite vaccine candidates, ready for scale up.
- Computational biology
 - Infrastructure in place, ready for scale up.